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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SMITH, CAROLYN L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/087,898	OLEK ET AL.
	Examiner	Art Unit
	Carolyn L. Smith	1631

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31 and 35-42* is/are pending in the application.

4a) Of the above claim(s) *35-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and remarks, filed 6/15/05, are acknowledged. Amended claims 1-31 are acknowledged.

Applicant's arguments, filed 6/15/05, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1-31 are herein under examination.

Claims Rejected Under 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

These rejections are necessitated by amendment.

Claim 1 recites the limitation "said individual, tissue, cell, or other biological material containing DNA" in lines 9-10. There is insufficient antecedent basis for this limitation in the claim as it is unclear if it is referring to the "individual, tissue, cell, or other biological material containing DNA" from step (a) or (b) which are not necessarily the same. Clarification of this

issue via clearer claim wording is requested. Claims 2-31 are also rejected due to their dependency from claim 1.

Claim 1 recites the limitation "said individual" in lines 5-6 and 9-10. There is insufficient antecedent basis for this limitation in the claim. Lines 4 and 8 recite "at least one individual" which means that there can be more than one individual. In this scenario of multiple individuals, it is unclear which individual is being referred to in the "said individual" limitation. It is also unclear if the phrase "at least one individual" in steps (a) and (b) are referring to the same at least one individual. Clarification of this issue may be rectified by amending the limitation to "said at least one individual." Clarification of this issue via clearer claim wording is requested. Claims 2-31 are also rejected due to their dependency from claim 1.

Claims 14 (line 3) and 15 (line 3) recite the phrase "associated with" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered "associated with". Clarification of the metes and bounds of the claims via clearer claim wording is required.

Claims 17 (line 2) and 25 (line 2) recite the phrase "dependent upon" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered "dependent upon". Clarification of the metes and bounds of the claims via clearer claim wording is required.

Applicants state that the claims have been revised and are now definite. The newly amended phrases mentioned above are indefinite for the reasons given above.

Claim Rejections – 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-11, 13-21, 23-26, 28, and 31 are rejected under 35 U.S.C. 102(e)(2) as being anticipated by Laird et al. (P/N 6,331,393 B1).

This rejection is maintained.

Laird et al. disclose a method for determining methylation patterns (biological effect or activity) in genomic DNA (containing genes) after being treated with sodium bisulfite (sample A) (chemical substance) (abstract), as stated in instant claims 1, 9, and 13. Laird et al. disclose methylation amounts in a sample are quantitatively determined based on reference to a control reaction (sample B) (col. 5, lines 61-64) which represents an unexposed sample and analyzing methylation levels in samples A and B, as stated in instant claim 1. Laird et al. disclose using probes and primers to distinguish between methylated and unmethylated nucleic acid, amplifying the DNA, and detecting methylated DNA via fluorescence-based quantitative PCR (col. 5, lines 16-64) which represents selecting sites differentially methylated. Figures 7 and 8 display data that represent a knowledge base generated based on the conclusive effect of sodium bisulfite treatment, as stated in instant claim 1. The gene names (i.e. ESR1 or MyoD1) in Figures 7 and 8 represent additional information used for the conclusion data found in these figures (i.e.

correlation between MLH1 gene expression, MSI status, and promoter methylation status of MLH1 in Figure 8, col. 24, lines 30-31), as stated in instant claim 24. The x-axes in the 2 graphs of represent at least two individual rows of analyses, as stated in instant claims 17 and 25. This data presentation also shows all or a part of the sites used for the conclusion, as stated in instant claim 23. Further conclusions are drawn by Laird et al. (col. 24, lines 48-67).. Laird et al. disclose in higher order eukaryotic organisms, DNA is methylated only at cytosines located 5' to guanosine in the CpG dinucleotide (col. 1, lines 14-17) which represents cytosine methylation. Laird et al. disclose contacting a DNA sample from a patient with a modifying agent, bisulfite (col. 5, lines 19-20 and 31). Laird et al. disclose various methods to identify altered methylation sites in cancer cells (col. 3, lines 3-5) and determining DNA methylation patterns at specific loci (col. 4, lines 12-15) which represents only one set of selected sites, as stated in instant claim 18. Laird et al. disclose selecting genes (col. 19, line 5) which represents a knowledge base of different classes, as stated in instant claim 19. Laird et al. disclose using PCR, sequencing, fluorescent labeling (col. 7, lines 26-65), as stated in instant claim 9. Laird et al. disclose using human colorectal adenocarcinoma (cancer) and normal mucosa (healthy) tissue samples (Figures 7 and 8; col. 22, lines 46-49), as stated in instant claims 4 and 5. Laird et al. disclose 25 match-paired normal and tumor samples with MLH1 expression level and MLH promoter methylation as well as MYOD1 control gene (Figure 8 and col. 8, line 64 to col. 9, line 12) which represent at least two methylation sites selected and analyzed in parallel, as stated in instant claims 11 and 21. Laird et al. disclose using parallel reactions with methylated, unmethylated, and control oligos of bisulfite-treated DNA samples (col. 18, lines 36-39). Laird et al. disclose analyzing methylation status of the ESR1 locus in DNA samples which is a gene that contains

hypermethylatable CpG islands that undergo de novo methylation in human colorectal tissue in all normal and tumor samples (col. 18, line 67 to col. 19, line 17 and col. 22, lines 29-30) which represents methylation sites are located in methylation relevant genes associated with cancer, as stated in instant claim 14. Laird et al. disclose using PCR primers and probes used for sequences representing fully methylated and fully unmethylated DNA in several genes, including ESR1 (col. 19, lines 32-40), which represents analyzing all potential methylation sites of the DNA, as stated in instant claim 10. Laird et al. disclose isolating DNA via proteinase K digestion from sperm and HCT116 (human colorectal cell line), treated with sodium bisulfite, and then the DNA samples are analyzed by COBRA analysis or amplification process using fluorescence-based real-time quantitative PCR (col. 16, line 55 to col. 17, line 17), as stated in instant claims 6-8. Laird et al. disclose that altered DNA methylation pattern of cytosine residues is mutagenic (col. 2, lines 34-36) which demonstrates that the colorectal samples mentioned above represent genes associated with ulcerative colitis which is a type of colon disease, as stated in instant claim 15. In Example 4, Laird et al. disclose analyzing the methylation DNA samples from the same patient (col. 22, lines 29-32) which represents analyzing methylation sites that are personalized, as stated in instant claims 16 and 28. In Example 5, Laird et al. disclose using 25 patients with tumor and normal tissue samples surgically removed (dissected tissue immediately frozen) (col. 23, lines 28-37) which represents histologically, dissected biological material from healthy and diseased individuals in instant claims 2-4. Laird et al. disclose the use of paraffin embedded samples (col. 9, lines 42-46). Laird et al. disclose using the TaqMan, Lightcycler, Sunrise technologies, as well as ABI Prism 7700 Sequence Detection System (col. 14, lines 5-20) which represent

selection at least partially performed automatically by an automate or computer device and conclusions performed by a computer system, as stated in instant claims 20, 26, and 31.

Thus, Laird et al. anticipate the limitations in claims 1-11, 13-21, 23-26, 28, and 31.

Applicants reiterate the rejection as well as amended claim 1. Applicants argue that Laird et al. do not disclose a method comprising the steps of obtaining a biological sample A what was exposed to at least one drug, chemical substance and/or pharmaceutical composition; obtaining sample B that was not exposed to at least one drug; chemical substance and/or pharmaceutical composition; and then analyzing the level of cytosine methylation at chosen sites of the DNA contained in the samples A and B. This statement is found unpersuasive as Laird et al. disclose treating genomic DNA with sodium bisulfite and comparing it to a control (see above 35 USC 102 rejection. It is further noted that instant claim 1 does not state that biological sample A was exposed and biological sample B was exposed, but rather the individual, tissue, cell or other biological material containing said DNA was either exposed or not exposed.

Applicants argue that sodium bisulfite does not constitute the claimed drug, chemical substance and/or pharmaceutical composition. This statement is found unpersuasive as sodium bisulfite is a chemical substance. Furthermore, Applicants did not provide any clear and complete definition of "chemical substance" in the originally filed disclosure that would exclude sodium bisulfite.

Applicants again submit that claim 1 requires biological sample A be exposed to the claimed drug, that the biological sample B not be exposed to the claimed drug and that the level of cytosine methylation in samples A and B be analyzed. Again, it is noted that instant claim 1

does not state that biological sample A was exposed and biological sample B was exposed, but rather the individual, tissue, cell or other biological material containing said DNA was either exposed or not exposed. It is further noted that the claims state that exposure or non-exposure can be to a drug, chemical substance and/or pharmaceutical composition, not necessarily only a drug. Applicants argue that Laird et al. do not disclose exposing Sample A to sodium bisulfite and not exposing Sample B to sodium bisulfite and then analyzing cytosine methylation after exposure or non-exposure to sodium bisulfite. This is found unpersuasive as instant claim 1 does not state that the steps must be performed in a particular order (i.e. before and after), but rather that the method comprises the steps.

Applicants argue that the specification notes that one of the principal purposes of the present invention is to provide a method for determining the effect of a drug, chemical substance and/or pharmaceutical composition on the methylation pattern of DNA. It is noted that limitations from the specification cannot be read into the claims unless that limitation is specifically recited in the claims. Applicants argue that Laird et al. teach sodium bisulfite treatment has no such effect as it does not alter the methylation state of DNA. Applicants did not point to where this passage is found, but it is noted that instant claim 1 recites concluding "the biological effect and/or activity". It is noted that the claims do not recite whether the effect is direct or indirect. It is noted that having no effect is a possible conclusion about biological effect and/or activity while performing a scientific experiment. In addition, methylation amounts quantify an "activity". Applicants have recited terms, such as "biological effect" and "activity" in instant claim 1 which have been broadly and reasonably interpreted. Applicants argue that Laird et al. do not disclose step (b). This statement is found unpersuasive as a control reaction

(col. 5, lines 61-64) represents an unexposed sample. Applicants' arguments are deemed unpersuasive, such that the 35 USC 102 rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The Central Fax Center number for official correspondence is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549.

MARJORIE A. MORAN
PRIMARY EXAMINER

August 8, 2005